REMARKS

Claims 86, 91-96, 98-100, 108, 113-118, 120-122, 133 and 134 were pending in the application. Claims 92, 94, 96, 114, 116 and 118 have been cancelled without prejudice and claims 86, 93, 108, 115, 133 and 134 have been amended. Therefore, claims 86, 91, 93, 95, 98-100, 108, 113, 115, 117, 120-122, 133 and 134 are currently pending. No new matter has been added.

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of and/or amendments to the claims are being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The cancellation of and/or amendments made to the claims are not related to any issues of patentability.

Rejection of Claims 86, 91, 93-95, 96, 98-100, 108, 113, 115-117, 120-122, 133 and 134 under 35 U.S.C. §112, second paragraph

Claims 86, 91, 93-95, 96, 98-100, 108, 113, 115-117, 120-122, 133 and 134 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner asserts that "the terms 'glutamate excitotoxicity, spin traps, growth factor, nicotinamide, ICE inhibitors, neuroimmunophilis, antioxidants, lipoic acid, cofactors, riboflavin, CoQ_{10}' are ambiguous."

Applicants respectfully traverse. The above-mentioned terms are found throughout the specification and at least at page 3, line 28 through page 4, line 6 of the specification and are terms well known in the art. Specifically, inhibitors of glutamate excitotoxicity are described (see, page 3, lines 32-34) as compounds which affect glutamate uptake and biosynthesis modulation, such as gabapentin and Riluzole. The term "spin trap" is a term recognized in the art as a compound which reacts with free radicals to form stable complexes, and is defined in the specification at page 39, line 21 through page 40, line 30. The term "growth factor" is defined as CNTF, BDNF and IGF-1 (see, page 3, line 34). Nicotinamide is well known in the art as a synonym of vitamin B_3 and is described in the specification at page 36, line through page 37, line 30. The term "antioxidants" is also well known in the art and is defined in the specification at page 41, line 14, through page 42, line 7. Lipoic acid describes a specific chemical compound that a skilled artisan would have known at the time of the invention. The term "riboflavin" is a well known synonym for vitamin B_2 is described in the specification at page 36, line through page 37, line 30. The term "CoQ10" is a well known abbreviation for coenzyme Q10 and is defined in the specification at page 37, line 32 through page 39, line 19.

Moreover, this rejection is moot as it pertains to the terms ICE inhibitors, neuroimmunophilis and cofactors in view of the amendments to the claims.

Accordingly, a skilled artisan would not find these terms ambiguous. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of the claims under 35 U.S.C. §112, second paragraph.

Rejection of Claims 86, 91, 93-95, 98, 100, 108, 113, 115-117, 120-122, 133 and 134 under 35 U.S.C. §102(e)

Claims 86, 91, 93-95, 98, 100, 108, 113, 115-117, 120-122, 133 and 134 are rejected under 35 U.S.C. §102(e) as being anticipated by Blass *et al.* (U.S. Patent No. 6,537,969). Specifically, the Examiner asserts that Blass *et al.* discloses "the method for treating diseases of the nervous system including Parkinson's disease, Huntington's disease using the same pharmaceutical composition of the instant claims" and "the same pharmaceutical composition combining creatine and a neuroprotective agent as the instant claims."

Applicants respectfully traverse. Independent claims 86, 108, 133 and 134 of the present invention are directed to methods for treating Parkinson's disease or Huntington's disease in a subject by administering creatine, a creatine phosphate or a creatine compound and a neuroprotective agent.

In contrast, Blass *et al.* teaches methods of and compositions for treating disorders associated with impaired mitochondrial function. Specifically, the compositions taught by Blass *et al.* include sugar, a Krebs cycle intermediate (*e.g.*, citric acid, aconitic acid, isocitric acid, α-ketoglutaric acid, succinic acid, fumaric acid, malic acid, oxaloacetic acid) or a salt thereof, or a precursor of a Krebs cycle intermediate. Blass *et al.* further teaches that the compositions may include an adjuvant for enhancing mitochondrial function, wherein the adjuvant includes vitamins (*e.g.*, vitamins B_1, B_2, B_6 and pantothenic acids), minerals (*e.g.*, calcium, magnesium, sodium, potassium and zinc), antioxidants (*e.g.*, ascorbic acid, α-tocopherol, resveratrol and quercetin) and other metabolism-enhancing compounds (*e.g.*, creatine and L-carnitine).

However, Blass *et al.* does not teach or suggest the combination of creatine, a creatine phosphate or a creatine compounds and a neuroprotective agent for the treatment of Parkinson's disease or Huntington's disease, as claimed in claims 86, 108, 133 and 134. Further, although Blass *et al.* teaches the use of creatine as a metabolism-enhancing adjuvant that may be included in a pharmaceutical composition containing a sugar and a Krebs cycle intermediate or a Krebs cycle intermediate precursor, Blass *et al.* does not teach or suggest methods of treating Parkinson's or Huntington's disease by administering creatine and a neuroprotective agent to a

subject. Moreover, Blass *et al.* does not teach or suggest neuroprotective agents selected from the group consisting of inhibitors of glutamate excitotoxicity, 2,3 dimethoxy-5-methyl-6-decaprenyl benoquinone, nicotinamide, spin traps, nitric oxide synthase inhibitors, cyclooxygenase 2 inhibitors, aspirin, N-acetylcysteine, antioxidants, lipoic acid, riboflavin, and CoQ10, as claimed in the present invention.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. §102(e).

Rejection of Claim 99 under 35 U.S.C. 103(a)

Claim 99 is rejected under 35 U.S.C. §103(a) as being unpatentable over Blass *et al.* (U.S. Patent No. 6,537,969). Specifically, the Examiner asserts that Blass *et al.* "generically disclosed pharmaceutical composition combining of creatine and a neuroprotective agent...and that the difference between the instant claims and the prior art is that the prior art has 2 active ingredients combining creatine and a neuroprotective agent whereas the instant claimed compositions has one additional neuroprotective agent or creatine compound." The Examiner concludes that "[o]ne having ordinary skill in the art would be motivated to modify the pharmaceutical composition of Blass *et al.* by adding one additional neuroprotective agent or creatine compound to obtain the instant claims."

Applicants respectfully traverse. Claim 99 is directed to methods for treating Parkinson's disease by administering to a subject creatine, a creatine phosphate or a creatine compound, a neuroprotective agent and at least one additional neuroprotective agent or creatine compound.

As described above, Blass *et al.* teaches methods of and compositions for treating disorders associated with impaired mitochondrial function, wherein the compositions include sugar, a Krebs cycle intermediate or a salt thereof, or a precursor of a Krebs cycle intermediate, and optionally an adjuvant for enhancing mitochondrial function.

Blass *et al.* do not teach or suggest the presently claimed methods of treating Parkinson's disease by administering to a subject creatine, a creatine phosphate or a creatine compound in combination with a neuroprotective agent. Neither does Blass *et al.* teach or suggest the neuroprotective agents disclosed in independent claims 86 and 133, on which claim 99 depends. Further, Blass *et al.* does not teach or suggest a therapeutically effective amount of creatine for the treatment of Parkinson's disease. Therefore, Blass *et al.* does not teach or suggest all the claim limitations. Moreover, Blass *et al.* would not have provided motivation for a skilled

artisan to develop the claimed methods. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. 103(a).

Rejection of Claims 86, 91, 93-95, 98-100 and 133 under 35 U.S.C. §112, first paragraph

Claims 86, 91, 93-95, 98-100 and 133 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that "the pharmaceutical art is unpredictable," "the instantly claimed invention is highly unpredictable," and that "applicant has [no] guidance or examples for treating Parkinson's disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent."

Applicants respectfully traverse. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). As the Examiner points out, there are eight factors to be considered when determining whether there is sufficient evident to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d, 1440, 1404 (Fed. Cir. 1988).

State of the Prior Art

The Examiner asserts that the 3-NP model of Parkinson's disease is not predictable. Applicants respectfully submit that the specification teaches the MPTP model, not the 3-NP model, for Parkinson's disease (see, Example 2, page 54, line 10 through page 56, line 10 of the specification). Furthermore, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has

evidence that the model does not correlate. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

The Examiner also asserts that "[t]he state of the of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities..." Applicants respectfully submit that it is routine practice in the pharmaceutical art to test compounds against animal models exhibiting symptoms of the disorder to be treated by said compounds. Furthermore, in vivo testing is preferable to in vitro testing in order to determine any detrimental side effects.

The Level of Skill in the Art

Applicants respectfully submit, and the Examiner acknowledges, that the level of skill in the art is high.

Amount of Guidance and Existence of Working Examples

The Examiner asserts that "applicant has no guidance or examples for treating Parkinson's disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent." Applicants respectfully traverse.

Claims 86, 91, 93-95, 98-100 and 133 are directed to ***methods for treating*** Parkinson's disease by administering creatine, a creatine phosphate or a creatine compound and a neuroprotective agent. Applicants respectfully submit that a skilled artisan in possession of the specification would have readily been able to determine the structure of creatine, a creatine phosphate or a creatine compound. A skilled artisan would have also been able to identify appropriate neuroprotective agents from the specification. Further, the specification discloses specific amounts of several neuroprotective agents and creatine compounds that have been used in the prior art. Moreover, Applicants respectfully submit that Example 2 discloses detailed methods for screening creatine, a creatine phosphate or a creatine compound in mice subjected to MPTP-induced Parkinsonian syndrome, along with methods for determining the affect of these compounds on the mice. In addition, MPEP § 2164.01(c) states that

> it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.

Accordingly, a skilled artisan would have been able to use the specification to make and use the methods of treating Parkinson's disease in a subject by administering creatine, a creatine phosphate or a creatine compound and with neuroprotective agent.

Therefore, when considered in light of these factors, the present specification demonstrates that a skilled artisan would have been able to use the claimed invention at the time of filing without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 108, 113, 115-117, 120-122 and 134 under 35 U.S.C. §112, first paragraph

Claims 108, 113, 115-117, 120-122 and 134 are rejected under 35 U.S.A. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner asserts that "the pharmaceutical art is unpredictable" and that "applicant has [no] guidance or examples for treating [Huntington's] disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent."

Applicants respectfully traverse. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Moreover, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). As the Examiner points out, there are eight factors to be considered when determining whether there is sufficient evident to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d, 1440, 1404 (Fed. Cir. 1988).

State of the Prior Art

The Examiner asserts that the 3-NP model of Huntington's disease is not predictable. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004). Applicants respectfully submit that the 3-NP model was considered an appropriate model for Huntington's disease at the time the application was filed, as evidenced by Fontaine *et al. J. Neurol.* 75 (2000) 1709-1715 (see Abstract) and Vis *et al. Neuropathology and Applied Neurobiology* 27 (2001) 68-76 (see Abstract) (Appendices A and B, respectively).

The Examiner also asserts that "[t]he state of the of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities..." Applicants respectfully submit that it is routine practice in the pharmaceutical art to test compounds against animal models exhibiting symptoms of the disorder to be treated by said compounds. Furthermore, in vivo testing is preferable to in vitro testing in order to determine any detrimental side effects.

The Level of Skill in the Art

Applicants respectfully submit, and the Examiner acknowledges, that the level of skill in the art is high.

Amount of Guidance and Existence of Working Examples

The Examiner asserts that "applicant has no guidance or examples for treating Huntington's disease using pharmaceutical composition of a combination of creatine, creatine phosphate or a creatine compound and a neuroprotective agent." Applicants respectfully traverse.

Claims 108, 113, 115-117, 120-122 and 134 are directed to ***methods for treating*** Huntington's disease by administering creatine, a creatine phosphate or a creatine compound and a neuroprotective agent. Applicants respectfully submit that a skilled artisan in possession of the specification would have readily been able to determine the structure of creatine, a creatine phosphate or a creatine compound. A skilled artisan would have also been able to identify appropriate neuroprotective agents from the specification. Further, the specification discloses specific amounts of several neuroprotective agents and creatine compounds that have been used in the prior art. Moreover, Applicants respectfully submit that Example 1 discloses detailed methods for screening creatine, a creatine phosphate or a creatine compound in mice subjected

to malonate and 3-NP induced Huntington's disease, along with methods for determining the affect of these compounds on the mice. In addition, MPEP § 2164.01(c) states that

> it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph.

Accordingly, a skilled artisan would have been able to use the specification to make and use the methods of treating Huntington's disease in a subject by administering creatine, a creatine phosphate or a creatine compound and with neuroprotective agent.

Therefore, when considered in light of these factors, the present specification demonstrates that a skilled artisan would have been able to use the claimed invention at the time of filing without undue experimentation. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

SUMMARY

It is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conference with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: November 28, 2006

Respectfully submitted,

By _____

Cynthia M. Soroos
Registration No.: 53,623
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant